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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,412	01/22/2001	Ruowen Ge	1781-0215P	7335

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,412	GE ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8,10,13-16,19,20,22,23 and 25-29* is/are pending in the application.

4a) Of the above claim(s) *10,15,16,20 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-8, 13, 14, 19, 22, 28 and 29* is/are rejected.

7)☒ Claim(s) *25-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, REMARKS, STATUS OF THE APPLICATION AND CLAIMS

1. The amendment and response filed 2/14/05 are acknowledged, entered and considered. In view of Applicant's request claims 22, 23 and 28 have been amended. Claims 1, 2, 6-8, 10, 13-16, 19, 20, 22, 23 and 25-29 are pending in the application of which claims 10, 15, 16, 20 and 23 are withdrawn as non-elected invention for the reasons of record. Thus, the Office action is directed to the merits of claims 1, 2, 6-8, 13, 14, 19, 22 and 25-29 as *per* elected invention. Applicant is again advised to cancel non-elected invention. The rejection under 35 U.S.C. 112, first paragraph for claims 22 and 28 is maintained for the reasons of record. Claims 1, 2, 6-8, 13, 14, 19, 25-27 and 29 were indicated as allowable in the previous Office action, however, a review of the claims reveal that the claims do not comply with requirements of 35 U.S.C. 112, first paragraph. Thus, the allowance of claims 1, 2, 6-8, 13, 14, 19, 25-27 and 29 are withdrawn. Also, the Finality of the previous Office action is withdrawn in view of withdrawing the allowance and the following new ground of rejection as set forth *infra*.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no description in the instant specification for

The claimed methods of **preventing or treating a subject** for the conditions being claimed, such as primary tumor growth or metastasis by inhibiting tumor angiogenesis (claims 22 and 28) as currently amended.

Applicant's arguments filed 2/14/05 have been fully considered but they are unpersuasive. Applicant has argued that typical of the claims in question is claim 23. The claims in question do not recite that tumors are being prevented (nor do they recite that a subject is being prevented). Instead, the claims recite (in part) that the **growth or metastasis** of tumors that already exist in a subject ("a subject presenting a tumor) is treated or prevented. Thus, the invention in question involves (among other things) preventing tumor growth or metastasis. Further, Applicant argues that the specification describes the claimed invention and cites page 8, lines 6-11 for the effective doses of the peptides administered is unpersuasive. Contrary to Applicant's arguments, the typical of the claims in question is not claim 23 (claim 23 is withdrawn as non-elected invention); rather, the claims in question are claims 22 and 28. As argued by Applicant, the claims are not directed to inhibit and/or prevent the existing tumor from further growth. They are directed to prevent or treat primary tumor growth or metastasis.

Applicant's attention is directed to the definition of metastasis on page 945 of Dorland's Illustrated Medical Dictionary, Twenty-fifth Edition, published by W.B. Saunders, 1974 which defines **metastasis** as the transfer of diseases from one organ or part to another not directly connected with it. It may be due either to the transfer of pathogenic microorganisms (e.g., tubercle bacilli) or transfer of cell, as in malignant tumors. The capacity of metastasize is a characteristic of all malignant tumors. Thus, in view of the known definition of metastasis, there is no written description for *in vivo* showing for the effectiveness of the peptides as claimed nor there is a recognized model (identified as useful) being treated according to methods of **preventing or treating a subject** for the conditions being claimed (i.e., preventing or treating primary tumor growth or metastasis).

With respect to Applicant's assertion that the enclosed reference of Ueda et al (Oral Oncol., Vol. 35, No. 6, pp. 554-560, 1999) shows the *in vivo* effectiveness of the peptides as claimed in a recognized model for methods of **preventing or treating a subject** for the conditions being claimed is unpersuasive. Contrary to Applicant's assertion, what Applicant has shown in the instant specification and the references cited to support Applicant's assertion is: infection + anti-angiogenic agents (e.g., portion of endostatin protein or TNP-470) = treatment ***and not*** infection + anti-angiogenic agents + prevention as asserted and claimed because for the **prevention** to occur, one must establish an infection + protocol (anti-angiogenic agents) with passage of time resulting in immune response or inhibition as in current case = **prevention**. Further, Applicant's claims are directed to prevention, and there is no objective factual evidence in the

specification or references enclosed or cited by Applicant to show that prevention has occurred since no adequate time was given to mimic the protocol administered in the animal models and allow evaluation of active immune response or inhibition. Thus, one cannot administer at the point of infection and claim preventing or treating a subject for the conditions claimed without appropriate testing for the reasons discussed above.

The followings are new grounds of objection and rejection:

OBJECTION TO THE SPECIFICATION

3. On page 4, line 19, the instant specification states that other preferred peptides are shown in Table 1 (SEQ ID NOS:29-50). However, there is no disclosure of Table 1 in the instant specification. Similar problem has been noticed on parent application Serial Number 09/385,442, now U.S. Patent No. 6,200,954 B1. Appropriate correction is required.

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

4. Claims 1, 2, 6-8, 13, 14, 19, 22 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no description in the instant specification for the claimed peptide comprising a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and

contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the peptide as claimed in independent claim 1.

The breadth of claim 1 is broad and encompasses unspecified variants regarding the length from 7-20 amino acids long and containing a pair of proline residues penultimate to a terminus of the peptide. No reference sequence has been provided. There is no written description indicating the claimed variants for the peptide containing a pair of proline residues at least one of which is a terminal residue penultimate to a terminus of the peptide having 7-20 amino acid length except for the elected invention of the peptide having the amino acid sequences of SEQ ID NO:30. There are no written description for other peptides comprising a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the peptide being made or used in the instant specification.

The use of 7-20 amino acid residues with any peptide comprising a portion of an endostatin protein suggests that the amino acid sequence/residue intended to be modified by substitution is either is not known or Applicant contemplates modification of a portion of an endostatin protein by substitution from 0 to 20 of amino acid residues in the peptide. Thus, the scope of the claims is not commensurate with the written description and/or enablement provided by the disclosure with regard to the amino acid residues identified by substitution of 7-20 amino acid residues with any portion of an endostatin protein for the following reasons:

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspect of the protein is extremely complex. While it is known that amino acid substitution is generally possible in any given protein the positions within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of success are limited. Other positions in the sequence are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis and in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only relatively conservative substitutions or no substitutions (See e.g., Bowie et al., Science, Vol. 247, 1990, pp. 1306-1310, especially page 1306, col. 2, paragraph 2). Similarly, Houghten et al., teach the relative importance of position and individual amino acid residues in peptide antigen-antibody interactions. The reference shows that a protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Detailed examinations of other antibody-antigen systems are being carried out to establish the existence of general trends in peptide antigen recognition patterns (See e.g., Houghten et al., Vaccines 86, Cold Spring Harbor Laboratory, 1986, pp. 21-25, especially page 24, last paragraph).

Further, Applicant has provided a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the

peptide as disclosed in SEQ ID NO:30. From this Applicant is attempting to extrapolate to a broad diversity of a portion of an endostatin protein bearing little relationship to an endostatin comprising SEQ ID NO:30 disclosed in the specification by claiming the substitution of any amino acid residue having less than 20 amino acids in length. Thus, in claim 1, any number of amino acids (at least from 0 to 20) can be replaced with any number ranging from 7-20 conservative or non-conservative substitution by insertion and/or deletion. The effects of this are unknown for the reasons discussed above, and as such, when this variable is added, the claimed invention becomes little more than conjecture. Moreover, without guidance and/or written description, the changes which can be made in the peptide/protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessary and improperly, extensive and undue. See Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 927 F.2d, 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Therefore, the scope of a peptide comprising a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the peptide disclosed in the instant specification would involve substitution of the amino acid residues in the portion of an endostatin protein with any number of amino acid residues ranging from 7-20 conservative or non-conservative. Hence, it would include those that have not been shown or taught or described to be useful or enabled by the disclosed method of making ad using the invention. Moreover, undue

experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since any number of amino acid residues ranging from 7-20 are to be substituted with any amino acids identified as an endostatin protein are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Thus, without guidance and/or written description through working example(s), one of ordinary skill in the art would not predict from the sequence data disclosed in the instant specification to substitute any number of amino acid residues with a range of at least 7-20 amino acids and be used as a pharmaceutical formulation by administering a therapeutically effective amount of said pharmaceutical formulation to treat or prevent primary tumor growth or metastasis in a subject in the manner claimed in the instant invention of claims 1, 2, 6-8, 13, 14, 19, 22 and 29.

Therefore, the specification does not disclose one reasonable method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. The specification lacks guidance/direction and/or written description as to how employ a peptide comprising a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the peptide in the manner as claimed in the instant invention.

In summary, the scope of the claims is broad, the written description does not demonstrate the claimed variants of endostatin protein or peptide having 7-20 amino

acid long, the effects of the claimed peptide is unpredictable, and the teachings or the written descriptions in the specification are limited, therefore, it is necessary to have additional guidance and/or written description to carry out further experimentation to assess the effects of a peptide comprising a portion of an endostatin protein, wherein said peptide is of length from 7-20 amino acids long and contains a pair of proline residues at least one of which is a terminal residue or a residue penultimate to a terminus of the peptide in the manner claimed in the instant invention of claims 1, 2, 6-8, 13, 14, 19, 22 and 29.

OBJECTIONTO CLAIMS, ALLOWABLE SUBJECT MATTER

5. Claims 25-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

CONCLUSION AND FUTURE CORRESPONDANCE

6. Claims 1, 2, 6-8, 13, 14, 19, 22, 28 and 29 are rejected, claims 25-27 are objected and claims 10, 15, 16, 20 and 23 are withdrawn as non-elected invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272 0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
March 24, 2005